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Methods

Alcohol use behaviors

We defined average alcohol consumption as the number of alcoholic beverages of any type consumed per week as derived from the physician-directed questionnaire at the index examination. We defined risky weekly drinking as ≥ 8 drinks per week for women and ≥ 15 drinks per week for men¹. Alcohol use frequency was assessed by asking: “Over the past year, on average, on how many days per week did you drink an alcoholic beverage of any type?” for Third Generation participants. We asked Offspring participants the average number of days per week they drank either beer, red wine, white wine, or liquor. We considered the most number of drinking days of any beverage type as the drinking frequency. We assessed the usual quantity consumed by asking: “Over the past year, on a typical day when you drink, how many drinks do you have” for Third Generation participants only (not asked in Offspring participants). Women who consumed more than one drink/drinking day and men who consumed more than two drinks per drinking day were classified as drinking in excess of the U.S. dietary guidelines.² We recorded the maximum drinks in last month by asking: “what was the maximum number of drinks you had in a 24 hour period during the past month” for the Third Generation participants. We asked Offspring participants their usual maximum limit of alcohol by alcohol type. We considered the maximum drinks as the highest maximal limit of alcohol across beverage types. For Third Generation participants we defined binge drinking as drinking 4 or more (for women) or 5 or more (for men) alcoholic beverages in a 24-hour period in the last month or answering yes to the question “since your last exam, has there been a time when you drank 5 or more alcoholic drinks of any kind almost daily.” For Offspring participants, binge drinking was defined as a maximum

limit of 4 or more drinks for women or 5 or more drinks for men. Responses were grouped into 2 categories (no vs yes binge drinking). We divided non-drinkers into former drinkers and never drinkers. For Third Generation participants, we identified former drinkers with the question “at what age did you stop drinking” and any participant that reported an age less than the current age was considered a former drinker. For Offspring participants, we identified former drinkers as any participant who reported consuming at least 1 drink/week on any prior exam (exam 1-6). For a secondary analysis, we considered the specific type of alcoholic beverage consumed, specifically wine, beer, liquor/spirit drink use, or combinations thereof. A respondent’s primary beverage type was on the basis of the largest number of drinks consumed during the past week on a beverage-specific basis.

Computed Tomography Liver Fat Measurement

In brief, 25 contiguous 5-mm-thick slices (120 kVp, 400mA, gantry rotation time 500 ms, and table feed 3:1) in the abdominal region (covering 125 mm above S1) were obtained from participants in the supine position using an 8-slice CT scanner (LightSpeed Ultra, General Electric, Milwaukee, WI). A calibration phantom (Image Analysis, Lexington, KY) was placed under each participant and present for all images obtained.

Covariates

We defined current smoking use as smoking at least one cigarette per day in the year preceding the FHS examination. We measured physical activity by the physical activity index score.³ We assessed education as a categorical variable (<12 years, high school graduate, some college, college graduate, or graduate degree). We accounted

for diet quality using a modified Mediterranean-Style Diet Score (MDS), which we have previously utilized in the FHS.⁴ The MDS consists of 9 components including: vegetables, fruits, nuts, legumes, whole grains, fish, red meat, ratio of monounsaturated fatty acids to saturated fatty acids, and alcohol.⁵ We modified the MDS to use just the first 8 components and eliminate the alcohol component given our study design. The scores for each component of the MDS range from 0-3 from lowest to highest quartile (except for red meat, which ranges from 0-3 from highest to lowest quartile). We summed all the score components (range 0-24), with higher scores indicating a healthier diet pattern. For Offspring Cohort participants, education was assessed at the second examination visit (1979–1983). We assessed income as a categorical variable of household income/year. For Offspring Cohort participants, income data was obtained from the third examination (1983–1987) and adjusted for inflation to 2003 (correction factor of 71%). Offspring Cohort participants were at a mean age of 48 years when income information was collected which is similar to the age of the Third Generation Cohort participants at their first examination (2002–2005) (mean age 40 years). Trained technicians used standard protocols for measuring heart rate, blood pressure, height, weight, and waist circumference (in inches) at the examination visits. We measured serum total and high density lipoprotein cholesterol (**HDL-c**), triglycerides, and glucose on fasting morning blood samples.⁶ We defined low HDL-c as <50 mg/dL for women and <40 mg/dL for men. We defined elevated triglycerides as triglycerides ≥150 mg/dL. We defined elevated blood as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of anti-hypertensive medication. We defined impaired fasting glucose as a fasting glucose ≥110mg/dL or treatment with a hypoglycemic agent or insulin.

Results

Continuous Liver Phantom Ratio as Outcome Measure

Overall, results were similar when we considered continuous LPR as the dependent variable though frequency of alcohol use was no longer associated with liver fat among drinkers in Model 2 and maximum drinks in 24 hours was no longer associated with liver fat among drinkers in Model 1 (**eTable 1**). For the beverage type specific analyses, results were overall similar when we considered continuous LPR as the dependent variable, though the associations with liver fat for liquor/spirit drinkers was no longer significant (**eTable 2**).

Sensitivity Analysis

We performed a sensitivity limiting the sample to Third Generation Cohort participants only (n=1687). Overall, the magnitude and direction of the associations were similar among Third Generation Cohort participants for the associations between alcohol use patterns and both hepatic steatosis (**eTable 3**) and continuous liver fat (**eTable 4**) though most associations were no longer statistically significant.

References

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4. Ma J, Hennein R, Liu C, et al. Improved Diet Quality Associates With Reduction in Liver Fat, Particularly in Individuals With High Genetic Risk Scores for Nonalcoholic Fatty Liver Disease. *Gastroenterology*. 2018;155(1):107-117.
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eTable 1: Multivariable-adjusted linear regression models for the association between various drinking patterns and more liver fat (-LPR), overall and among drinkers only

	Overall (n=2475)		Drinkers only (n=2002)	
	Model 1	Model 2	Model 1	Model 2
Alcohol use pattern*	β , 95% CI, p value	β , 95% CI, p value	β (95% CI); p value	β (95% CI); p value
Alcohol drinks per week	0.002 (-2.7E-05, 0.004); 0.05	0.003 (-0.00003, 0.004); 0.05	0.002 (0.00004, 0.005); 0.05	0.003 (0.001, 0.005); 0.007
Risky weekly drinking [†]				
Yes	0.006 (-0.0003, 0.013); 0.06	0.008 (0.002, 0.015); 0.01	0.006 (-0.0003, 0.013); 0.06	0.008 (0.002, 0.014); 0.01
No	reference	reference	reference	reference
Frequency (# drinking days/week)	0.0007 (-0.001, 0.003); 0.52	0.002 (-0.0003, 0.004); 0.10	0.001 (-0.001, 0.003); 0.42	0.002 (-0.0004, 0.004); 0.10
Usual quantity** (# drinks /drinking day)	-0.00004 (-0.002, 0.002); 0.97	0.001 (-0.002, 0.003); 0.33	0.002 (-0.001, 0.004); 0.27	0.0008 (-0.002, 0.003); 0.29
Usual consumption in excess of dietary guidelines ^{†,**}				
Yes	0.002 (-0.003, 0.007); 0.40	0.002 (-0.003, 0.007); 0.44	0.002 (-0.003, 0.008); 0.41	0.002 (-0.003, 0.007); 0.48
No	reference	reference	reference	reference
Max drinks in 24 hours in last month	0.002 (-0.0002, 0.004); 0.07	0.003 (0.0004, 0.005); 0.04	0.002 (-0.0003, 0.005); 0.08	0.003 (0.0002, 0.005); 0.03
Binge drinking [†]				
Yes	0.004 (-0.001, 0.009); 0.15	0.005 (-0.0002, 0.01); 0.06	0.006 (0.0002, 0.011); 0.04	0.006 (0.001, 0.012); 0.02
No	reference	reference	reference	reference
Non-drinkers				
Former drinkers	reference			
Never drinkers	-0.005 (-0.02, 0.009); 0.76	-0.002 (-0.02, 0.01); 0.75		

*For continuous alcohol use behaviors, betas are modeled per standard deviation increase in the continuous independent variable.

Model 1 is adjusted for age, sex, cohort, smoking, physical activity, education, and income.

Model 2 is adjusted for Model 1 and the components of the metabolic syndrome (waist circumference, low HDL-c, high triglycerides, elevated blood pressure, or impaired fasting glucose).

[†]Risky weekly drinking was defined as ≥ 8 drinks per week for women and ≥ 15 drinks per week for men. Usual consumption above US Dietary Guidelines was defined as ≥ 2 drink/drinking day for women or ≥ 3 drinks/drinking day for men. Binge drinking was defined as > 4 drinks for women or > 5 drinks for men in 24 hours.

**Third Generation Participants only

eTable 2: Multivariable-adjusted linear regression models for the association between various drinking patterns and more liver fat (-LPR), by alcohol type*

	Beer drinkers		Wine drinkers		Spirit drinkers	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Alcohol use pattern**	β , 95% CI, p value	β , 95% CI, p value	β , 95% CI, p value	β , 95% CI, p value	β , 95% CI, p value	β , 95% CI, p value
Alcohol drinks per week	0.006 (0.001, 0.011); 0.014	0.006 (0.002, 0.01); 0.005	0.002 (-0.002, 0.005); 0.33	0.002 (-0.002, 0.005); 0.37	-0.001 (-0.010, 0.007); 0.76	0.0008 (-0.007, 0.009); 0.85
Risky weekly drinking [†]						
Yes	0.020 (0.006, 0.034); 0.005	0.019 (0.006, 0.033); 0.004	0.003 (-0.006, 0.012); 0.51	0.005 (-0.004, 0.013); 0.3	-0.008 (-0.029, 0.013); 0.46	-0.007 (-0.027, 0.013); 0.49
No	reference	reference	reference	reference	reference	reference
Frequency (# drinking days/week)	0.002 (-0.003, 0.007); 0.40	0.004 (-0.0011, 0.008); 0.13	-0.0003 (-0.004, 0.003); 0.87	-0.0003 (-0.004, 0.003); 0.88	0.004 (-0.005, 0.01); 0.39	0.006 (-0.002, 0.01); 0.16
Usual quantity*** (# drinks /drinking day)	0.003 (-0.002, 0.008); 0.28	0.002 (-0.004, 0.007); 0.54	-0.0003 (-0.004, 0.004); 0.89	-0.001 (-0.005, 0.003); 0.63	0.002 (-0.008, 0.013); 0.66	-0.0004 (-0.010, 0.009); 0.94
Usual consumption in excess of dietary guidelines ^{†,***}						
Yes	0.008 (-0.003, 0.019); 0.17	0.007 (-0.003, 0.017); 0.17	0.0002 (-0.008, 0.008); 0.95	-0.001 (-0.009, 0.007); 0.79	0.009 (-0.011, 0.029); 0.37	0.004 (-0.015, 0.023); 0.66
No	reference	reference	reference	reference	reference	reference
Max drinks in 24 hours in last month	0.009 (0.004, 0.014); 0.001	0.008 (0.003, 0.012); 0.001	0.001 (-0.002, 0.005); 0.47	0.001 (-0.002, 0.005); 0.43	-0.003 (-0.012, 0.005); 0.46	-0.002 (-0.010, 0.006); 0.67
Binge drinking [†]						
Yes	0.019 (0.009, 0.029); <0.001	0.018 (0.008, 0.027); <0.001	0.002 (-0.008, 0.011); 0.74	0.001 (-0.007, 0.01); 0.76	-0.02 (-0.038, 0.004); 0.11	-0.01 (-0.034, 0.006); 0.18
No	reference	reference	reference	reference	reference	reference

For continuous alcohol use behaviors, betas are modeled per standard deviation increase in the continuous independent variable.

*Beer, wine, and spirit drinkers were defined as reporting consuming beer, wine, or spirits in the highest amount of any alcoholic beverage type consumed in a week. Participants consuming equal amounts of beer, wine, or spirits were excluded from this analysis.

**Model 1 is adjusted for age, sex, cohort, smoking, physical activity, education, and income.

Model 2 is adjusted for Model 1 and the components of the metabolic syndrome (waist circumference, low HDL-c, high triglycerides, elevated blood pressure, or impaired fasting glucose).

[†]Risky weekly drinking was defined as ≥ 8 drinks per week for women and ≥ 15 drinks per week for men. Usual consumption above US Dietary Guidelines was defined as ≥ 2 drink/drinking day for women or ≥ 3 drinks/drinking day for men. Binge drinking was defined as > 4 drinks for women or > 5 drinks for men in 24 hours.

***Third Generation participants only (n=1687)

eTable 3: Multivariable-adjusted logistic regression models for the association between various drinking patterns and hepatic steatosis (LPR ≤ 0.33) (Third Generation only)

	Model 1		Model 2	
Alcohol use pattern*	AOR, 95% CI	p value	AOR, 95% CI	p value
Alcohol drinks per week	1.06 (0.93,1.20)	0.41	1.13 (0.97, 1.30)	0.11
Risky weekly drinking [†]				
Yes	1.12 (0.73, 1.71)	0.60	1.28 (0.81, 2.04)	0.29
No	reference		reference	
Frequency (#drinking days/week)	1.00 (0.94, 1.07)	1.0	1.04 (0.97, 1.12)	0.24
Maximum drinks in 24 hours in the last month	1.14 (1.00, 1.30)	0.05	1.18 (1.02, 1.36)	0.03
Binge drinking [†]				
Yes	1.12 (0.84, 1.50)	0.43	1.19 (0.87, 1.63)	0.27
No	reference		reference	
Non-drinkers				
Former drinkers	0.41 (0.16, 1.01)	0.08	0.45 (0.17, 1.22)	0.14
Never drinkers	reference		reference	

*For continuous alcohol use behaviors, odds ratios are modeled per standard deviation increase in the continuous independent variable.

Model 1 is adjusted for age, sex, cohort, smoking, physical activity, education, and income.

Model 2 is adjusted for Model 1 and the components of the metabolic syndrome (waist circumference, low HDL-c, high triglycerides, elevated blood pressure, or impaired fasting glucose).

[†] Risky weekly drinking was defined as ≥ 8 drinks per week for women and ≥ 15 drinks per week for men. Binge drinking was defined as > 4 drinks for women or > 5 drinks for men in 24 hours.

eTable 4: Multivariable-adjusted linear regression models for the association between various drinking patterns and more liver fat (-LPR) (Third generation only)

	Model 1		Model 2	
Alcohol use pattern*	β (95% CI)	p value	β (95% CI)	p value
Alcohol drinks per week	0.002 (-0.0008, 0.004)	0.17	0.003 (0.001, 0.005)	0.02
Risky weekly drinking [†]				
Yes	0.005 (-0.003, 0.012)	0.23	0.007 (-6.32E-05, 0.014)	0.05
No	reference		reference	
Frequency (#drinking days/week)	0.00002 (-0.002, 0.002)	0.98	0.002 (-0.001, 0.004)	0.17
Maximum drinks in 24 hours in the last month	0.002(-0.0002,0.005)	0.08	0.003 (0.0004, 0.005)	0.02
Binge drinking [†]				
Yes	0.004 (-0.001,0.009)	0.15	0.005 (0.0001,0.01)	0.04
No	reference		reference	
Non-drinkers				
Former drinkers	-0.013 (-0.033, 0.007)	0.22	-0.008 (-0.03, 0.01)	0.41
Never drinkers	reference		reference	

*For continuous alcohol use behaviors, betas are modeled per standard deviation increase in the continuous independent variable.

Model 1 is adjusted for age, sex, cohort, smoking, physical activity, education, and income.

Model 2 is adjusted for Model 1 and the components of the metabolic syndrome (waist circumference, low HDL-c, high triglycerides, elevated blood pressure, or impaired fasting glucose).

[†] Risky weekly drinking was defined as ≥ 8 drinks per week for women and ≥ 15 drinks per week for men. Binge drinking was defined as > 4 drinks for women or > 5 drinks for men in 24 hours.